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From mouse to man: Predicting biased effects of beta-blockers in asthma

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From mouse to man: predicting biased effects of beta-blockers in asthma

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Conflict of interest statement: BJL has received previous grant support from the Chief Scientist Office, Scotland to evaluate effects of propranolol in patients with persistent treated asthma. BJL has also received unrestricted grant support from Chiesi, Meda, Almirall and Teva to evaluate small airways in persistent asthma and COPD; as well as multi-centre pharmaceutical support from Astra Zeneca, Teva, Janssen and Roche. In addition BJL has received personal payment for consultancy and advisory boards with the following pharmaceutical companies: Astra Zeneca, Chiesi, Teva, Boehringer Ingelheim and Meda. BJL has also received personal payment for giving speaker talks with Chiesi, Teva, Meda and Mitsubishi Tanabe as well as support to attend educational meetings from Chiesi, Boehringer Ingelheim and Teva. WJA has no conflict of interest and PMS has no conflict of interest.

We read with interest the elegant data from (Thanawala *et al.*, 2015) in ovalbumin sensitized epinephrine deficient or wild type mice which suggested differential effects of biased signaling with propranolol and nadolol. We were particularly intrigued by the observation in epinephrine deficient mice whereby there was a disconnect between propranolol and nadolol in restoring the asthma phenotype compared to controls. It is tempting to simplistically extrapolate these data in mice to what might happen in human subjects with asthma in order to explain the negative effects of propranolol on airway hyper-responsiveness (AHR), reported in two separate placebo controlled double blind trials in patients receiving inhaled corticosteroids (ICS), which were powered to detect a one doubling dilution difference in the provocative concentration of methacholine (n=18) or histamine (n=16) to produce a 20% fall in forced expiratory volume in 1s (i.e. the PC20 FEV1 threshold) (Anderson *et al.*, 2014; Short *et al.*, 2013). In this regard, in patients with persistent asthma, the PC threshold for FEV1 is closely related to PC threshold for airway resistance (Short *et al.*, 2015).

Upon close inspection of the data for methacholine AHR (Thanawala *et al.*, 2015), the provocative concentration to induce a 100% increase (PC100 threshold) in airway resistance was unaltered in wild mice (n=6) treated with propranolol in contrast to an increase with nadolol (n=7). The blunting of methacholine AHR with nadolol which was statistically significant ($P<0.05$) amounting to approximately a 0.6 doubling dilution shift compared to vehicle treated mice (n=10). Such an effect in mice with nadolol on AHR would be considered clinically irrelevant in human patients as it less than the minimal important difference of one doubling dilution shift in PC threshold. It is therefore difficult to extrapolate the magnitude of this effect with nadolol on methacholine AHR in mice to what has previously been reported in two unblinded studies with nadolol in human asthmatic subjects which amounted to an approximate two doubling dilution shift in methacholine PC20, albeit in mild intermittent asthmatics who were not taking ICS (Hanania *et al.*, 2010; Hanania *et al.*, 2008).

It is however unclear how the relative mg dose per body weight of propranolol in mice (80-140mg/L in water) equates to that in humans (80mg slow release tablet /day). Moreover if propranolol at usual therapeutic doses of 80mg/day does indeed confer arrestin independent partial agonist activity at the ERK1/2 activation pathway in humans then one might expect to see an increase in TH2 mediated inflammatory biomarkers. For example in persistent asthmatics there was no worsening in eosinophils, eosinophilic cationic protein or exhaled breath nitric oxide when oral propranolol 80mg/day was added to a low dose of ICS, while a higher dose of ICS in conjunction with oral placebo produced further suppression of the same TH2 biomarkers (Anderson *et al.*, 2014).

Moreover asthma control and disease specific quality of life were also unaltered by propranolol (Anderson *et al.*, 2014; Short *et al.*, 2013).

In order to properly confirm the putative beneficial effects of biased inhibitory signaling in mice this will require a placebo controlled trial to demonstrate clinically relevant improvements in methacholine PC20, inflammatory markers and asthma control with nadolol on top of existing ICS therapy in persistent asthma. The placebo controlled clinical trial (clinicaltrials.gov

NCT01804218) evaluating effects of nadolol in ICS naïve mild intermittent asthmatics will unfortunately not answer this clinically important question.

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